Cotranslational folding of the voltage-gated K^+ channel KvAP

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During translation, the nascent chain is subjected to fluctuations in tension that are related to, among other things, membrane insertion of hydrophobic segments[1]. Relative tension can be measured by Force Profile Analysis, in which protein fragments are genetically coupled to an arrest sequence and one measures the fraction of protein that is released during translation by nascent chain tension[2]. Voltage-gated channels are of particular interest in membrane protein folding because they contain the voltage-sensing S4 helix. S4 contains a series of conserved arginine residues (RxxRxxRxxR), which are critical for its function. It was previously shown that, despite the high polarity of this segment, S4 is just hydrophobic enough to insert[3]. However, how this occurs is not fully understood. In this study, we measured the force profile for a well-studied archaeal voltage-gated K^+ channel, KvAP. Our data shows that the S4 region of the force profile is marked by previously unobserved decreases in tension which are unusual for transmembrane domains (Fig. 1). By modifying the sequence with mutations or truncations, we show that these decreases in tension are strongly dependent on the arginine residues of S4, but also other more distant residues in the sequence. Taking into account the rest of the force profile, we propose a new, high-resolution model for stepwise insertion of KvAP which may also be applicable to other voltage-sensing domains.

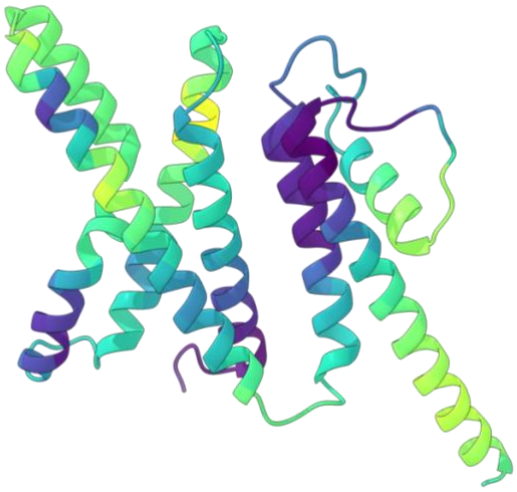

Figure 1. Force profile mapped onto structure. PDB: 6UWM is shown colored by fraction of full-length protein, where high values are light and low values are dark.

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3. Hessa, T., White, S. H. & von Heijne, G. Membrane insertion of a potassium-channel voltage sensor. *Science* **307**, 1427 (2005).